The Peritumoral Zone in Diffuse Low-Grade Gliomas

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Contributor: Melissa Silva , Catalina Vivancos , Hugues Duffau

Diffuse low-grade gliomas (DLGGs) are heterogeneous and poorly circumscribed neoplasms with isolated tumor cells that extend beyond the margins of the lesion depicted on MRI. Efforts to demarcate the glioma core from the surrounding healthy brain led to define an intermediate region, the so-called peritumoral zone (PTZ).

low-grade glioma peritumoral zone surgery brain connectome

1. Introduction

As the name states, diffuse low-grade gliomas (DLGG)—World Health Organization (WHO) grade 2 diffuse astrocytic and oligodendroglial tumors [1]—are in essence poorly circumscribed and intrinsically heterogeneous [2][3][4][5] tumors that progressively infiltrate the brain. Regardless of the common initial slow growth rate, these tumors will ineluctably become more aggressive with malignant transformation if left untreated [6].

Concerning their typical features on routine magnetic resonance imaging (MRI), they may even seem somewhat delineated T1-hypointense and T2- and FLAIR-hyperintense lesions, but in fact, this imaging technique only identifies the high-density tumor, underestimating the real spatial extent of the disease [7]. Indeed, it has clearly been shown that isolated tumor cells extend beyond the margins of the tumor depicted on MRI [8][9][10][11][12][13], leading to the concept of so-called peritumoral zone (PTZ) at the interface between the tumor core and the surrounding healthy brain.

Current studies are attempting to find physiological/metabolic imaging modalities that can help overcome this MRI limitation and thus correctly identify tumor limits [4][14][15][16], which would eventually lead to more accurate assessments on therapeutic goals and subsequently improve its results.

In fact, it has been evidenced that the extent of resection is a major prognostic factor, and hence, surgery is highly recommended in DLGG [17]. Furthermore, recent reports state that, when feasible, a “supratotal” resection (SpTR)—meaning a functional-guided resection beyond MRI signal abnormalities and therefore including the PTZ—may have an even greater impact on the natural history of the disease [12][18][19][20][21][22]. In this case scenario, it is also likely that adjuvant treatment, namely, chemo- and/or radiotherapy, could be postponed and thus further extend not only survival but, moreover, patients’ long-term quality of life (QoL) [23].

In addition, there has been increasing evidence that the associated epileptogenesis in DLGG is highly related to the increased and aberrant excitatory synapses observed in the peritumoral area [24][25][26][27][28][29], which makes it another therapeutic challenge, especially by supporting SpTR also for functional reasons since seizure control is strongly related to QoL.

2. DLGG Heterogeneity and Relation with the Surrounding Brain: The Peritumoral Zone (PTZ)

DLGGs (WHO grade 2 gliomas) are infiltrative tumors arising from glial cells of the brain that are traditionally classified according to their cell morphology—astrocytes, oligodendrocytes, or a combination of both. More recently, their categorization includes molecular features, especially IDH mutation and 1p19q codeletion status [1]. Indeed, the 2021 fifth edition of the WHO classification introduced major modifications that advance the impact of molecular diagnostics in brain tumor, it established different approaches to glioma nomenclature and grading, and it emphasized the importance of integrated diagnoses: new tumor types and subtypes were introduced based upon new diagnostic technologies, such as DNA methylome profiling [1].

Regarding glioma spatial structure, defined by its growth pattern, three main types are considered: solid tumor with no peripheral isolated tumor cells (ITCs), tumor tissue with peripheral ITCs, and ITCs within intact brain parenchyma (meaning no solid tumor) [30]. When analyzing the behavior of tumor cells' growth according to histology, it was found that oligodendroglial tumors with 1p19q loss tend to be more circumscribed lesions with a predominant proliferation in situ, in contrast to the more diffuse, infiltrative, and less bulky astrocytic ones [31]. In a study of histologically defined glial tumor growth patterns, those with mixed or "solid" growth patterns were also more likely to have 1p/19q loss, and those with infiltrative growth were more likely to have intact 1p/19q [32]. A more recent work demonstrated that DLGGs with sharp borders were more frequently IDH-mutant compared with tumors with indistinct borders [33].

When studying the intratumoral heterogeneity of DLGGs, within a WHO grade 2 tumor, there can be single or multiple microfoci of higher cellular or vascular density or even atypia (the presence of which was related to significantly lower survival) [3]. In a series of low-grade oligodendroglioma biopsies, it was found that in 62.5% of cases, the cycling cells formed a ring of proliferation in the peripheral areas of the tumor, whereas in the remaining cases the cycling tumor cell fraction increased toward the center of the tumor core, evidencing the heterogeneity of these tumors [2]. Additionally, concerning oligodendrogliomas, but using en bloc resected tumors, different tumor cell and vessel densities were identified throughout all the cases [4]. A more recent study revealed the existence of sparse, but widely distributed, protoporphyrin IX "hotspots" within low-grade gliomas, which exhibited some malignancy features, such as less differentiated cellular state, ability to divide, and metabolic reprogramming [5].

With the knowledge of isolated tumor cells within intact brain parenchyma, the concept of "peritumoral zone", mostly applied for glioblastomas [34], can also be used for DLGG to describe a peripheral area with the same macroscopic aspect of a normal brain but already with microscopic tumor infiltration. This is usually a radiological definition.

In fact, it is nowadays understood that DLGGs actually extend beyond MRI-defined abnormalities. In 1987, in a series of stereotaxic biopsies from glial neoplasms—which included 20 grade 2 lesions—the researchers took 5 samples from normal T2-weighted MRI regions surrounding grade 2 astrocytomas and in 3 of those cases found ITCs, admitting that “normal” brain tissue was rarely biopsied for ethical reasons [8]. Five years later, Watanabe et al., saw tumor cells already infiltrating brain tissue beyond the T2 high-intensity lesions delineated on MRI in 5 of their 8 low-grade-glioma cases [9]. When trying to determine the helpfulness of diffusion tensor imaging (DTI) in better identifying glioma margins, Price et al. (2006) found tumoral cells in 8 of the 18 patients in whom the biopsy trajectories were taken into peritumoral areas (with normal T2 signal intensity on MRI), but in their series, this was less seen in lower grades—1 of 7 cases [10]. In 2010, in a study of diffuse low-grade oligodendrogliomas, Pallud et al. (2010) collected biopsy samples from within and beyond the hypersignal areas on T2-weighted and FLAIR MRI sequences and found the presence of cycling cells beyond MRI-defined abnormalities in all patients—where a higher density of tumor cells was found at distances of 10 to 20 mm beyond the imaging limits but not at distances greater than 20 mm [11]. Similarly, Gerin et al. (2013) discovered cycling tumor cells infiltrating the parenchyma around the tumor core up to 20 mm outside the MRI-defined abnormalities [2]. In 2016, Zetterling et al., also found that tumor cells extended beyond the FLAIR MRI border in all the 5 cases of en bloc resection studied at a maximum distance of 1.4 cm from the radiological margin. Additionally, a common pattern of growth was noted, as the tumor cells followed the white matter (WM) tracts and were slightly more concentrated in the peripheral parts of the tracts [13]. Importantly, in a recent series using intraoperative image-guided biopsies, genetic analyses using RNA sequencing and whole-exome sequencing observed a gene expression pattern and mutational landscape of the PTZ that were distinct from that seen in the tumor core and peripheral brain tissue [15].

Studies on PTZ patterns of WM displacement and/or invasion may be important for understanding how much functional brain tissue is compromised, because invasion of the WM tract connectivity prior to surgery represents a main limitation of neuroplasticity [35]. Latini et al. (2021), when trying to understand whether specific features of the different WM pathways could reflect the differences in observed glioma infiltration, built a theory that a smaller fiber diameter, decreased fiber density and increased extracellular space may represent pathways of least resistance for glioma cell dissemination [36]. In the same spirit, a recent review on DLGG interaction with WM tracts suggested that myelin may constitute a protection against glioma cell migration; therefore, its nonexistence or destruction could result in fragility sites facilitating tumor invasiveness [37].

Regardless of the common initial slow growth rate, DLGG will finally become more aggressive with malignant transformation if left untreated [6]. That is the main reason why it is important to thoroughly understand intratumoral and peripheral cellular behavior and its complex interactions with neural networks.

3. FLAIR MRI Cannot Reflect the PTZ: How Can DLGG Delineation Be Improved?

Following the awareness of the conventional MRI’s inability to delineate DLGG’s real margins, several groups have explored physiologic and metabolic imaging modalities to surpass this limitation.

Radiomics, which aims at extracting multiple quantitative imaging features using reproducible algorithms, has been increasingly applied and represents the basis of radiogenomics, whose purpose is to determine the association between the collected imaging data and both genomic signatures and molecular phenotypes of gliomas [38][39]. Of note, there are emerging methods based upon a deep learning and radiomic model that could be promising for glioma grading using multiplanar reconstructed MR contrast-enhanced T1-weighted imaging [40].

For each unique MRI sequence, different maps can be generated, and contemporary studies are trying to figure out which one(s) is(are) most useful on a glioma study. Some well-known examples are apparent diffusion coefficient (ADC) maps from diffusion-weighted imaging (DWI); maps of fractional anisotropy (FA), mean diffusivity (MD), and kurtosis (K) from DTI; and regional cerebral blood volume (rCBV) maps from dynamic susceptibility contrast-enhanced (DSC) sequences.

Within the range of MRI sequences, DWI and DTI have been the most frequently used sequences to improve the detection of tumoral infiltration in both low- and high-grade gliomas (HGGs). In fact, DWI was included in the 2015 consensus recommendations as part of the minimum standard brain tumor imaging protocol [41]. ADC and MD values are considered indirect measures of tumor cellular density because proliferating tumor cells hamper the diffusion of extracellular water. Therefore, they estimate tumor proliferation in DLGG by inverse correlation. Of note, brain edema is an important confounder. Throughout the years, studies on this matter have been contradictory. A recent systematic review and meta-analysis concluded that ADC derived from DWI has a high diagnostic performance in differentiating low-grade from high-grade gliomas, underlining its easy accessibility and lower cost when compared with other metabolic and physiologic imaging [42]. However, the diagnostic accuracy regarding PTZ was not scrutinized, possibly because of the scarce literature focusing on this specific subject. Interestingly, a study on tumor proliferation that focused exclusively on DLGG found that the interval changes of ADC values correctly predicted disease progression (diagnostic accuracy of 86%) before apparent radiologic progression on conventional imaging [43], supporting the potential use of radiomics in detecting peritumoral cells.

Another explored technique is diffusion kurtosis imaging (DKI), an extension of DTI, which provides quantitative data on how tissue water diffusion deviates from a normally distributed diffusion. A prospective study published in 2017, which compared DKI parameters with perilesional normal-appearing white matter (NAWM) and contralesional NAWM, found some significant differences, namely, higher mean diffusivity and lower kurtosis in the perilesional WM, which were associated with tumor infiltration [14]. Some of the latest studies combining DWI and DKI parameters, despite including DLGG in their cohorts and evaluating the peritumoral area, essentially reinforced the ability of the techniques in differentiating DLGG from HGG but were unable to draw new conclusions regarding the PTZ in DLGG [44][45].

The DSC sequence, that is, a perfusion-weighted imaging (PWI) technique, identifies changes associated to neoangiogenesis, which correlate with malignancy. The resultant quantitative parameters (including rCBV) are potentially helpful in predicting grading, progression, and prognosis in DLGG, as documented in a 2015 systematic review [46]. A prospective pilot study with 10 subjects (4 with DLGG and 6 with HGG) used multimodal MRI to build a predictive model of tumor infiltration in glioma patients, including DTI and PWI quantitative metrics, that could

serve as a biomarker for nuclear density [47]. Another prospective work, from 2018, used multiparametric MRI from 7 patients (5 with DLGG and 2 with HGG) to assess each sequence's capacity to differentiate between tumor core, tumor infiltrated edema, and normal tissue. In this series, the only statistically significant MRI-derived feature able to differentiate tumor core from infiltrated edema was rCBV, with a specificity of 95%; however, it was not able to perform likewise in discerning tumor infiltrated edema from normal tissue [48].

Of note, using multicomponent T2-weighted MRI relaxometry (a method of myelin water imaging) in proton therapy, Bontempi et al., accidentally found that decomposing T2 can be more sensitive than conventional FLAIR imaging for detecting subtle tissue alterations in the peritumoral region of WHO grade 2 and 3 gliomas [16].

In addition to all these advanced MRI sequences, functional MRI (fMRI) and DTI tractographies are nowadays part of the presurgical imaging of DLGG in many institutions. Resting-state fMRI and advanced high angular resolution diffusion imaging (HARDI) tractography are refining these methods' results. They are useful in investigating cortical and subcortical plasticity and exploring the association between longitudinal functional changes and progression of disease [35][49][50]. One group recently reported the use of mean blood-oxygen-level-dependent (BOLD) signal from resting-state fMRI (rs-fMRI), coupled with conventional structural MRI, to compare not only with histology results but also with RNA sequencing and whole-exome sequencing of biopsy samples from tumoral (TT), peritumoral (PT), and healthy (HT) tissues. The researchers found that the mean BOLD signal was significantly associated with the molecular data (calculated expression similarity index of differentially expressed genes) in their determination of PT relative to HT and TT ($p < 0.001$). In their series, the average PT distance in DLGG was 10.9 mm with an 18% recurrence rate, whereas in HGG it was 8.75 mm with an 81% recurrence rate at the last follow-up. The Kaplan–Meier curves showed a significant difference in progression-free survival between patients with a PT distance ≤10 mm and >10 mm [15].

Moreover, positron emission tomography (PET) imaging, a noninvasive method of measuring biochemically specific targets of tumors (and more specifically PET imaging with labeled amino acid tracers), has been widely used to depict the biological activity of DLGG [4][51][52]. In a recent prospective study, Verberg et al., sought to determine, through multiregional biopsies, the most accurate imaging combination to detect glioma infiltration. In their series, fluoroethyl-L-tyrosine PET was not found to be a component of the optimal imaging combinations for nonenhancing glioma, and its diagnostic accuracy was lower than that of FLAIR MRI [53]. To the best of the knowledge, no other relevant studies have been published on the value of PET imaging in identifying the PTZ on DLGG. Additionally, the present limited availability of amino acid PET makes it a nonroutine imaging technique on glioma management.

Closing this topic, researchers highlight a 2021 systematic research on the integration of multimodality imaging and artificial intelligence to improve the visualization of tumor cell infiltration in glioma [54], which found only two articles that included DLGG (along with HGG) in their cohorts [47][53], depicting the gap between low-grade and high-grade research.

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